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Abstract

Individuals with tuberous sclerosis complex (TSC) are at increased risk of developing self-injurious behaviour. The persistence of this deleterious behaviour over years is reported in aetiologically heterogeneous samples to be between 60% and 80%, but is unknown for TSC. In this study we determined the three-year persistence of self-injury in a sample (n = 52) of children (with and without intellectual disability) and adults (with intellectual disability) with TSC, and examined characteristics associated with persistence. Findings for self-injury were contrasted to those for aggression and property destruction to examine the specificity of results to this behaviour. Self-injury was persistent in 84.6% of those with TSC who showed this behaviour, in contrast to 66.7% both for aggression and destruction. Persistent self-injury was associated with poor self-help skills, greater overactivity/impulsivity and more behavioural indicators of pain. These latter two characteristics were also associated with persistent aggression. No characteristics were associated with persistence of property destruction. These findings suggest that self-injurious behaviours in individuals with TSC, together with aggressive and destructive behaviours, are highly persistent and would benefit from targeted intervention. Poor adaptive skills, overactivity/impulsivity and painful health conditions may differentiate those at most risk for persistent self-injury or aggression.

Keywords: Tuberous sclerosis complex, self-injury, tuberous sclerosis associated neuropsychiatric disorders (TAND), aggression, property destruction.

Background

Tuberous sclerosis complex (TSC) is a rare genetic disorder associated with a range of highly variable physical and neuropsychiatric comorbidities. Reported prevalence of TSC is 1 in 10,000 (O'Callaghan et al. 1998), however it can occur very mildly and thus go undiagnosed, affecting the accuracy of prevalence estimates (Osbourne et al. 1991). TSC is caused by mutations of either *TSC1,* on chromosome 9q34 (van Slegtenhorst et al. 1997), or *TSC2* on chromosome 16p13.3 (European Chromosome 16 Tuberous Sclerosis Consortium, 1993). Loss of intracellular TSC1 or TSC2 protein leads to growth of benign tumours throughout the body including the kidneys, heart, skin, and brain. Epilepsy is reported in 79-87.9% of individuals (Joinson et al. 2003; Kopp et al. 2008), with seizure severity and seizure treatment impacting on intellectual development *(*Bolton et al. 2002; Chu-Shore et al. 2010*;* Joinson et al. 2003; O'Callaghan et al. 2004). A bimodal distribution of IQ is described; just over half of individuals have IQs in the typical range, 44% score below 70 (Joinson et al. 2003) and around 30% have an IQ below 21, indicative of profound intellectual disability (ID) (Prather & de Vries 2004).

The substantial proportion of the TSC population who have ID, and particularly the proportion with profound ID, should highlight this syndrome as one in which risk of self-injury and other adverse behavioural outcomes is likely to be elevated. Prevalence rates of 4% for self-injury and 7% for aggression have been reported in a total population study of individuals with ID across a range of aetiologies (Emerson et al. 2001). In a meta-analysis of risk markers for challenging behaviour, individuals with profound ID were more likely to show self-injury, as well as aggression and disruption of the environment, than those with mild-moderate ID (McClintock et al. 2003).

A recent review of tuberous sclerosis associated neuropsychiatric disorders (TAND) indicates that rates of self-injury, while varying considerably, are notably higher than those in

the general population of individuals with ID, ranging from 17 to 69% (Leclezio & de Vries 2015). Self-injury is evident across the lifespan in TSC. [Withheld for blind review] found rates of self-injury of 27% in a study of children and adolescents with TSC (with and without ID). Using the same measures with an adult sample (all of whom had ID) rates of self-injury were 31% (withheld for blind review). Rates of aggression are reported to be higher than self-injury and prevalence estimates are more consistent, from 51 to 66% (Leclezio & de Vries 2015). Factors relating to sample composition (degree of ID, presence of other TAND features) may contribute to variability in self-injury estimates. Interestingly, in a survey by de Vries et al. (2007) self-injury was significantly associated with the presence of ID but the same was not true of aggressive outbursts.

There are a number of additional features of TSC and TAND which are likely to contribute to increased risk of self-injury, and of other challenging behaviours. In addition to identifying the correlate of level of ID, McClintock et al. (2003) found that self-injury, aggression and property destruction were all more likely in those with autism spectrum disorder (ASD). ASD is a widely recognised feature of TAND, with a recent meta-analysis of ASD in genetic syndromes identifying prevalence estimates of ASD phenomenology of 36% in TSC (Richards et al. 2015). Estimates of ADHD, another feature of TAND, suggest 30-60% of individuals with TSC meet criteria (de Vries et al. 2007; Muzykewicz et al. 2007; Lo-Castro et al. 2011). Impulsivity and overactivity, typically associated diagnostic features of ADHD, are also strongly associated with self-injury and aggression in individuals with genetic syndromes associated with ID (Arron et al. 2011).

The numerous health problems associated with TSC also confer increased risk of self-injury. Renal angiomyolipomas may cause flank pain, and increased intracranial pressure resulting from subependymal giant cell astrocytomas can cause headaches. There is robust evidence that pain and illness are associated with self-injury (Carr & Owen-DeSchryver

2007) and that syndrome-related painful health conditions may be associated with increased rates of self-injury (e.g. gastroesophageal reflux in Cornelia de Lange syndrome, Luzzani et al. 2003).

Two recent studies have examined whether these potential risk markers were associated with self-injury and other challenging behaviours in children/adolescents and adults with TSC (withheld for blind review; withheld for blind review). Both studies used the same measures of demographic and behavioural characteristics, including ASD and ADHD symptomatology and pain-related behaviours. Presence of self-injury was associated with impulsivity and pain-related variables in both the child/adolescent and adult samples. In the child/adolescent sample self-injury was also associated with repetitive behaviours and overactivity, whereas in the adult sample self-injury was also associated with poorer social communication and poorer socialisation skills. For the child/adolescent sample, aggression was associated with the same broad characteristics as self-injury; however for the adult sample aggression was associated only with repetitive behaviour and impulsivity. It is noteworthy that impulsivity was associated with self-injury and aggression in both the child/adolescent and adult samples, suggesting it may be a particularly robust risk marker for adverse behavioural outcomes in TSC.

While there is evidence that there may be some stability of self-injury in TSC across the lifespan from cross-sectional data (withheld for blind review; withheld for blind review), it is not clear how stable this behaviour is longitudinally. Cooper et al. (2009a) examined self-injury in a sample of adults with ID over a two-year follow up period and reported persistent self-injury in 61.8% of their sample. Over a longer time period Emerson et al. (2001) reported a seven-year persistence rate of 71%, and an 84% persistence of self-injury over 20 years has been reported (Taylor et al. 2011). In terms of the specificity of the persistence of self-injury, Cooper et al. (2009b) also investigated persistence of aggression

and destruction of property in their sample. When compared to the 61.8% persistence rate of self-injury, both of these behaviours also had high persistence rates (68.4% for physical aggression and destruction of property at 70.6%).

To date no study has examined persistence of self-injurious behaviour in TSC, despite the fact that self-injury is a potentially highly deleterious behaviour, impacting on quality of life (Beadle-Brown et al. 2009), and caregiver well-being (Hastings 2003). If self-injury in TSC is persistent then it would be particularly important to target interventions to address this behaviour given that it is unlikely to resolve spontaneously. It would therefore also be of significant value to ascertain the characteristics associated with or predictive of persistent self-injury, to help identify those at greatest risk.

The current study evaluated the three-year persistence of self-injury in a sample of children (with and without ID) and adults (with ID) with TSC, following up samples published previously by [withheld for blind review] and examined risk markers that may identify those with persistent self-injury. To examine whether these findings were specific to self-injury or whether they generalised to other adverse behavioural outcomes, we also set out to contrast the findings for self-injurious behaviour with those for aggressive and destructive behaviours. There is some evidence that self-injury and aggression may dissociate in TSC (e.g. in terms of association with ID, de Vries et al. 2007), and so it is possible that persistence and/or risk markers may also differ across behaviours.

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Method

Recruitment

The time 1 (T1) sample was recruited from the UK family support group, the Tuberous Sclerosis Association, who posted questionnaire packs to their members. At time 2 (T2)

families were recruited from a database held by [withheld for blind review] of families from that sample who expressed an interest in taking part in future research. Of 87 participants who participated at T1, 73 consented to future contact. Where possible, these caregivers were contacted by phone to inform them of the study and obtain email addresses. Study information, including a link to online consent forms and questionnaires, were sent by email (where possible) or by post where neither email nor telephone contact was possible. Given the inappropriateness of requesting caregiver reports from adults who have the capacity to self-report, at T1 caregivers of individuals over the age of 16 were instructed to return the consent forms and questionnaire pack only if the person they cared for had ID. Therefore, the sample consisted of children under 16 years old with and without ID and of individuals aged over 16 years with ID. Individuals who turned 16 between T1 and T2 were included if they scored below the maximum score on the Wessex scale Self-Help subscale (Kushlick et al. 1973), indicating they likely had ID. Caregivers were required to indicate that they had a confirmed diagnosis of TSC from an appropriate professional (e.g. clinical geneticist, paediatrician) to be include in the study. Participants were excluded if no data was provided on the measure of challenging behaviour at T1.

Procedure

This study was subject to ethical review by (withheld for blind review). Invitations were distributed to caregivers, directing them to the online link to the study. Participants were also informed that they could request a paper copy of the questionnaire pack. The online study guided participants through the consent forms and questionnaires, with participants being able to save and return to the questionnaire if needed. The paper pack and the online study contained the same information and consent forms.

Participants

Fifty-two of the 70 participants eligible for inclusion at T2 consented to participate (21 were aged under 16 years, 31 were over 16 years), representing a return rate of 74.29%, and 59.77% of the total T1 sample. Within the T2 sample, of those aged under 16 years, 72.2% were described by caregivers as party able or able (compared to 'not able' on the Self-Help subscale of the Wessex Behaviour Scale) of those aged over 16 years 58.1% were described as able or partly able. To ensure that the T2 sample was not biased by loss of data from participants not included at T2, χ^2 and Mann-Whitney U analyses were carried out on T1 measures comparing participants included at T2 from those who declined to participate (test values reported in Table 1*).* No significant differences were found, indicating that the T2 sample was likely to be a representative sample of the original T1 participants.

Table 1: Demographic and behavioural data compared for participants at T2 compared to those who declined participation. Medians presented with interquartile (IQ) range.

		Participated at T2	Declined participation	Mann-Whitney U/ χ^2	Df	*p* value
N		52	32			
Age at T1	*Median (IQ range)*	16.13 (9.95-27.36)	19.5 (10.03-27.75)	789.50	-	.877
Gender	*% Male*	57.69	58.06	.001	1	.974
Vision	*% Normal*	82.69	96.88	3.80	1	.051
Hearing	*% Normal*	96.08	100	1.25	1	.264
Speech	*% Partly verbal/verbal*	75.00	74.19	.007	1	.935

Mobility	*% Ambulant*	76.92	71.88	.269	1	.604
Self-Help	*% Partly able/able*	65.38	64.52	.006	1	.936
Self-injury	*% Showing behaviour at T1*	52.00	30.00	.24	1	.623
Aggression	*% Showing behaviour at T1*	42.00	53.33	.97	1	.325
Destruction of property	*% Showing behaviour at T1*	24.00	40.00	2.29	1	.131
Overactivity/ impulsivity (TAQ total score)	*Median (IQ Range)*	27 (10-40.25)	28 (10-46.5)	661.50	-	.590
Mood (MIPQ total score)	*Median (IQ Range)*	33.5 (28-40.75)	36 (28.5-42)	686.50	-	.368
Repetitive behaviour (RBQ total score)	*Median (IQ Range)*	16 (6.29-23)	12 (8-26.75)	662.00	-	.594
ASD symptomatology (SCQ total score)	*Median (IQ Range)*	22 (15-27.5)	18 (14-25.5)	583.00	-	.187
Behavioural indicators of pain (NCCPC-R total score)	*Median (IQ Range)*	11 (5-20)	12 (6-20)	761.50	-	.781

Measures

The measure of challenging behaviour (self-injury, aggression and property destruction) used at T1 was repeated at T2. Additional measures described are those used at T1 to examine factors associated with persistent challenging behaviour. All measures were carer report questionnaires.

T1 and T2 measure

Challenging Behaviour Questionnaire (CBQ; Hyman et al. 2002): The CBQ assesses presence of challenging behaviour over the past month, including self-injury, physical aggression, and destruction of property. The measure has good reliability (inter-rater reliability coefficients range from 0.46 to 0.72, Hyman et al. 2002).

T1 measures

The Activity Questionnaire (TAQ; Burbidge & Oliver 2008): This measure assesses overactivity and impulsivity, two domains of the diagnostic criteria for ADHD according to DSM-V (American Psychiatric Association 2013). It has three subscales; Overactivity, Impulsivity, and Impulsive Speech. A total score reflecting Overactivity/impulsivity can be calculated. The TAQ has good inter-rater and test-retest reliability (Burbidge et al. 2010).

Mood, Interest and Pleasure Questionnaire (MIPQ; Ross et al. 2008): The MIPQ assesses two constructs associated with depression; Mood, and Interest and Pleasure, based on carer responses to 25 items. The sum of item scores provides an overall Mood, Interest and Pleasure score. It has strong reliability, both inter-rater and test-retest, and excellent internal consistency, including for use with individuals with profound intellectual and multiple disabilities (Ross & Oliver 2003).

Repetitive Behaviour Questionnaire (RBQ; Moss & Oliver 2008): This 19-item questionnaire assesses Stereotyped Behaviour, Compulsive Behaviour, Insistence on Sameness, Restricted Preferences, and Repetitive Speech. An overall Repetitive Behaviour score can be calculated for subscales. It has good reliability (Moss et al. 2009). Concurrent

validity, as tested against the repetitive behaviour subscale of the Autism Screening Questionnaire (Berument et al. 1999), was at a level of 0.6 ($p < .001$) (Moss et al. 2009).

Social Communication Questionnaire (SCQ; Rutter et al. 2003): Based on the Autism Diagnostic Interview (Le Couteur et al. 1989), the SCQ was developed originally as a screening tool for autism. The measure consists of three subscales; Communication, Social Interaction, and Repetitive and Stereotyped patterns of Behaviour. Scores from these three subscales form a total score. A total score of 15 or more on the SCQ is suggestive of ASD; 22 or greater suggestive of Autism (Berument et al. 1999).

Non Communicating Child Pain Checklist-Revised (NCCPC-R; Breau et al. 2004): This measure assesses behaviours indicative of pain. Carers indicate the frequency of behaviours across 30 items on a four point Likert scale, with responses summed to give a total score. The original administration of this measure requires raters to respond based on behaviour seen in the last two hours. In the current study this was changed to asking caregivers how often the individual with TSC showed behaviour in the last week, as a method of measuring “typical” pain behaviour, an approach employed in previous research including with adults (Symons et al. 2009).

Wessex Behaviour Scale (Kushlick et al. 1973): This measure was designed to give a rating of adaptive ability for children and adults with ID. The questions assess a variety of different behaviours and abilities and form five separate subscales; Self-Help Skills, Speech, Literacy, Mobility and Continence. For the current study the Self-Help total score, with a maximum of 9, was used.

Analysis

For each behaviour the following groups were formed based on the status of the behaviour across the two time points: absent (behaviour not reported at either T1 or T2), remission (behaviour shown at T1 but not at T2), incidence (behaviour not shown at T1 but reported at T2) and persistent (behaviour reported at both T1 and T2). To examine stability of behaviour over time McNemar analyses assessed those who showed each behaviour at T1 according to whether their behaviour was persistent or remitted. To evaluate whether persistence of self-injury differed from persistence of aggression and property destruction, Cochrane Q-tests were used, with the binary outcomes of persistent behaviour and all other behaviour categories (absent, remission and persistent).

The second goal was to identify putative risk markers which may identify those showing persistent self-injury (and to contrast these markers to those for aggression and property destruction). To achieve this, analyses were conducted between absent, transient (consisting of incidence and remission groups) and persistent groups on their total scores from the T1 behavioural measures (to avoid inflating type I error rates by analysing subscales from every measure). The Wessex Self-Help scores and age of the participant at T1 were also included as these factors showed significant differences between behaviour present and behaviour absent groups at T1 (see withheld for blind review). Average scores for the absent, transient and persistent behaviour groups were contrasted using Kruskal-Wallis tests. A more stringent alpha level of .01 for these omnibus tests was used. Where significant differences in these characteristics were found between groups, Mann-Whitney U tests were utilised to identity which groups differed from each another. For analyses involving the SCQ only participants aged over four were included in analyses (as this is the lower age limit of the measure).

Results

Persistence of self-injury compared to aggression and property destruction

At T2 32.7% (N=17) of individuals were reported to show self-injury, with reported frequency of aggression and destruction being similar (36.5%, N=19 and 30.8% N=16 respectively).

In terms of stability of self-injury over time, Table 2, shows that self-injury was absent at both time points for most participants. However, for those participants who did show self-injury it was most likely to be persistent, with a large majority of participants (84.6%) who exhibited self-injury at T1 still showing this behaviour at T2. This proportion was lower for aggression and destruction (both 66.7%), in a similar pattern, the majority of those showing these behaviours at T1 continued to show them at T2.

Table 2: Absence, remission, incidence and persistence of self-injury, aggression and property destruction, together with remission and persistence rates of those showing each behaviour at T1.

Behaviour	Absence	Remission	Incidence	Persistence	Remission in participants with behaviour at T1	Persistence in participants with behaviour at T1
Self-injury (N=52)	63.46% (33)	3.85% (2)	11.54% (6)	21.15% (11)	15.38% (2)	84.62% (11)
Aggression (N=50[a])	50.00% (25)	14.00% (7)	8.00% (4)	28.00% (14)	33.33% (7)	66.67% (14)

Destruction of Property (N=50 [a])	62.00% (31)	8.00% (4)	14.00% (7)	16.00% (8)	33.33% (4)	66.67% (8)

[a] Missing data from T1reduces the N in these analyses

McNemar analysis indicated that there were no significant differences in rates of behaviour reported at T1 and T2 for self-injury (p =.289), suggesting that self-injury was relatively stable across the three years. This finding was mirrored for aggression (p =.549) and destruction (p =.549).

Cochrane Q tests evaluated whether persistence of self-injury in TSC differed from persistence of aggression and property destruction. No significant difference in persistence (versus transience and absence combined) was observed across the three behaviours (Q(2) = 4.154, p = .125).

Potential risk markers for persistent self-injury, aggression and property destruction

Kruskal-Wallis tests indicated significant differences between the absent, transient and persistent self-injury groups in levels of T1 self-help ability, overactivity/impulsivity and behavioural indicators of pain (see table 3).

Table 3: Kruskall-Wallis analyses of differences across absent, transient and persistent groups for self-injury, aggression, and destruction of property on T1 behavioural measures with the Wessex Self-Help scale and Age at T1. *significant p ≤.01, ** significant p ≤ .001

	Self-injurious behaviour			Aggressive behaviour			Destruction of property		
Measure	χ^2	*df*	*p* value	χ^2	*df*	*p* value	χ^2	*df*	*p* value
TAQ	10.31	2	.006*	12.48	2	.002*	5.44	2	.066

MIPQ	6.03	2	.049	1.87	2	.393	3.56	2	.169
RBQ	3.46	2	.177	9.94	2	.007*	1.72	2	.422
SCQ	8.00	2	.018	1.58	2	.455	.20	2	.904
NCCPC-R	10.23	2	.006*	15.58	2	<.001**	5.37	2	.068
Self-Help	12.47	2	.002*	1.75	2	.417	2.26	2	.323
Age	.39	2	.824	3.31	2	.191	.31	2	.858

Figure 1 shows the pattern of differences across absent, transient and persistent self-injury groups for the characteristics for which group differences were found.

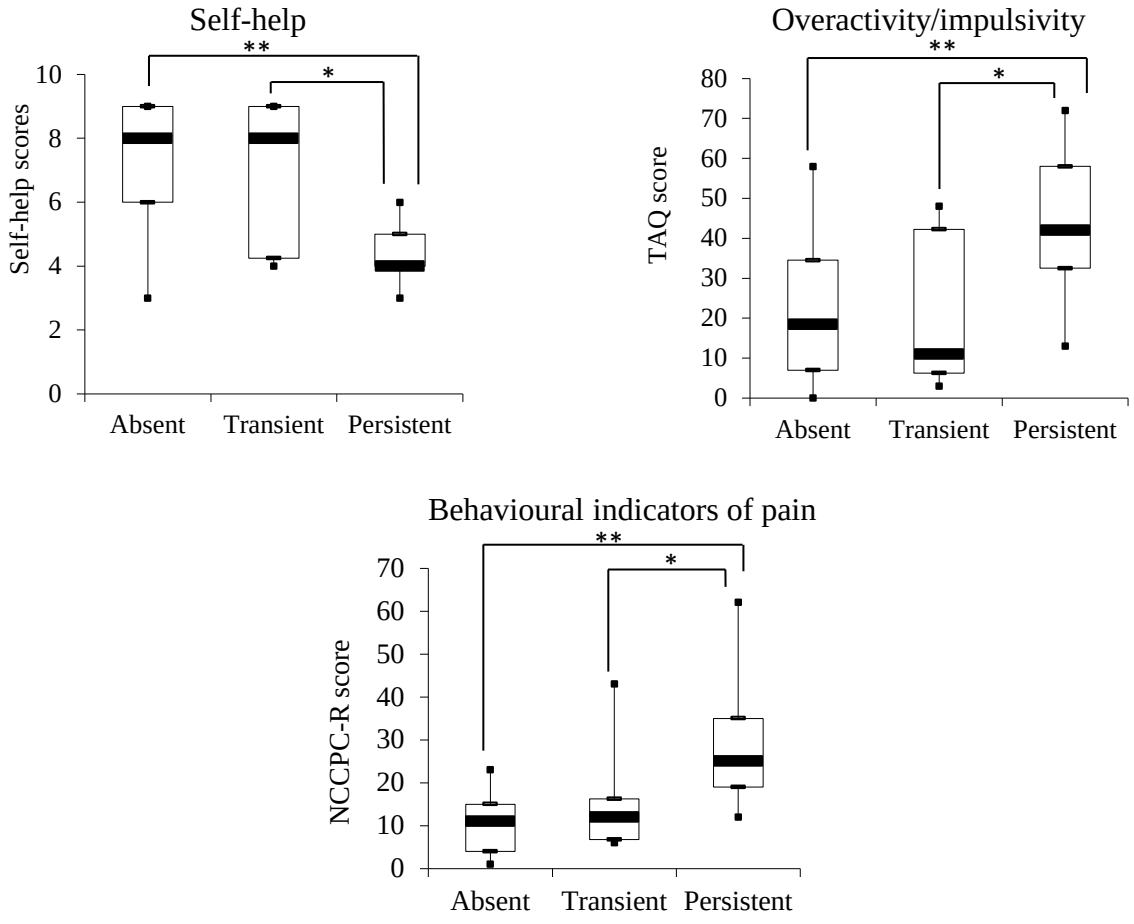
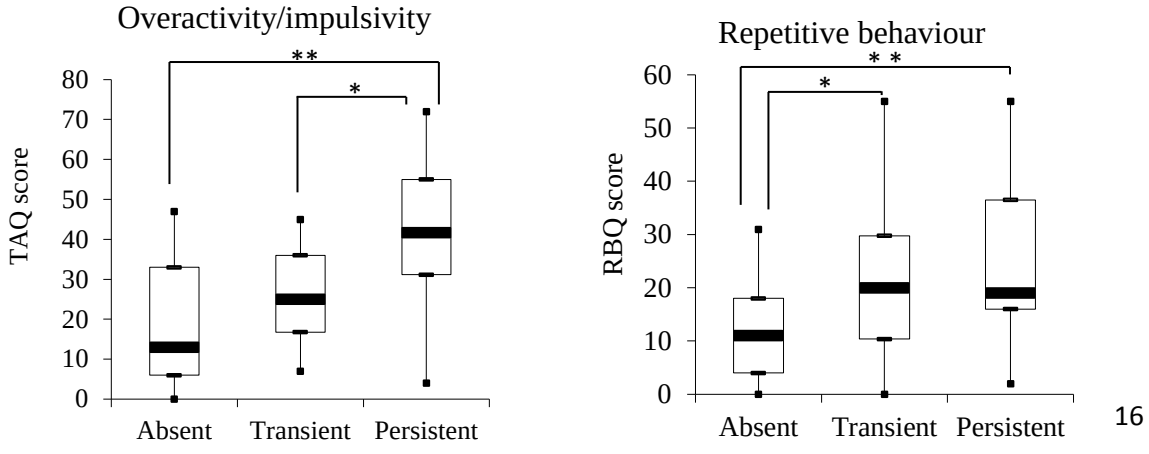


Figure 1: Median scores (plus minimum, maximum and 1st and 3rd quartiles) on T1 Wessex self-help scores, TAQ overactivity/impulsivity scores and NCCPC-R behavioural indicators of pain scores for absent, transient and persistent self-injury groups. * paired differences significant p <.05, ** paired differences significant p <.005

Mann-Whitney tests indicated that T1 overactivity/impulsivity and behavioural indicators of pain, were significantly greater (U = 60.5, p = .001 and U = 60.5, p = .001 respectively), and self-help ability significantly poorer (U = 54.5, p < .001) in participants with persistent self-injury versus those with absent self-injury. Participants with persistent self-injury also had higher T1 overactivity/impulsivity and more behavioural indicators of pain (U = 19.5, p = .043 and U = 20.00, p = .048) and poorer self-help skills (U = 17.5, p = .025) than those with transient self-injury. Participants with absent and transient self-injury did not differ on any T1 characteristics (p > .05).

Kruskall-Wallis analyses demonstrated that T1 overactivity/impulsivity levels and behavioural indicators of pain differed across the absent, transient and persistent aggression groups, as did repetitive behaviours (see table 3). Figure 2 shows the differences across the absent, transient and persistent aggression groups for these characteristics.



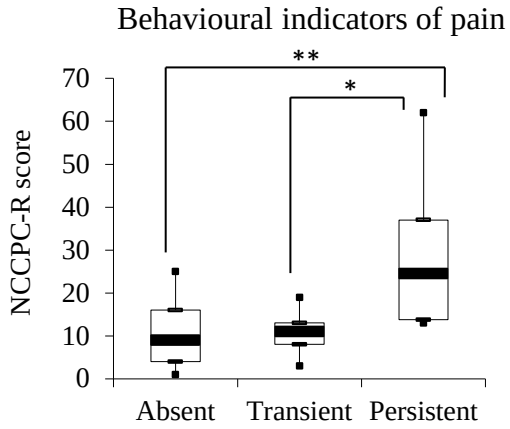


Figure 2: Median scores (plus minimum, maximum and 1st and 3rd quartiles) on T1 TAQ overactivity/impulsivity scores, RBQ repetitive behaviour scores and NCCPC-R behavioural indicators of pain scores for absent, transient and persistent aggression groups. * paired differences significant $p < .05$, ** paired differences significant $p < .005$

Mann-Whitney follow up analyses indicated that T1 overactivity/impulsivity ($U = 64.00$, $p = .001$), behavioural indicators of pain ($U = 43.50$, $p < .001$), and repetitive behaviour ($U = 74.00$, $p = .003$) were significantly greater in participants with persistent aggression than those with absent aggression. Participants with persistent aggression also had greater T1 overactivity/impulsivity and behavioural indicators of pain ($U = 34.50$, $p = .037$ and $U = 30.00$, $p = .01$ respectively) than those with transient aggression. Participants with transient aggression had higher T1 repetitive behaviour than those with absent aggression ($U = 71.50$, $p = .05$).

For destructive behaviours there were no differences across absent, transient and persistent groups in any of the T1 characteristics assessed ($p > .05$, see table 3).

Discussion

This was the first study to investigate the persistence of self-injurious behaviour in TSC and to contrast this to persistence of other adverse behavioural outcomes. Nearly 85% of individuals who showed self-injury continued to show this behaviour three years later, compared to just over 65% of individuals who continued to show aggression or property destruction. Self-help skills, overactivity/impulsivity and behavioural indicators of pain differentiated those who showed persistent self-injury from those for whom self-injury was absent or transient. These characteristics were similar to those that differentiated individuals showing persistent aggression. However, none of the characteristics examined differentiated individuals showing persistent property destruction.

Findings indicate that for individuals with TSC who show self-injury, this behaviour is highly likely to persist. While there was some fluctuation in self-injury (representing incidence or remission), analyses implicate remarkable stability over three years. The reported persistence of self-injury in this sample of children and adults with TSC is higher than some previous reports of self-injury persistence in populations with ID over a similar time frame. The 61.8% persistence rate in Cooper et al. (2009a) was over 20% less than in the current study. This may be attributable to their use of stricter criteria for recording presence of self-injury; they applied the Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities / Mental Retardation (DC-LD: Royal College of Psychiatrists 2001) to define presence of both self-injury and aggression. When persistence of self-injury in a sample of children and adults with ASD (with and without ID) was examined

using the same measure as that used in the current study, a three-year persistence rate of 77.8% was reported (Richards et al. 2016).

The persistence of self-injury was around 20% higher than the persistence of aggression and property destruction. Previous research reported a two-year persistence of aggression and property destruction of 68.4% and 70.6% respectively in adults with ID (Cooper et al. 2009b) and 15-18 month persistence of 69% for aggression and 57% for destruction in young children with severe ID (Davies & Oliver 2016). The persistence rates found in the current study for aggression and destruction are broadly consistent with this past research. However, in both these studies self-injury was less persistent than aggression (and property destruction in the Cooper et al studies), whereas in the current study self-injury was more persistent. Differences in age and level of ID across these samples may account for these inconsistencies.

Putative risk markers of poorer self-help abilities, greater overactivity/impulsivity and more behavioural indicators of pain differentiated individuals who showed persistent self-injury from those who did not (both those who had never shown self-injury and those whose self-injury was transient, groups who in turn did not differ from one another in these characteristics). Greater overactivity/impulsivity and more behavioural indicators of pain also differentiated those who showed persistent aggression from those who did not. It appears therefore that being overactive/impulsive and showing signs of pain might be particularly robust indicators of persistent adverse behavioural outcomes in individuals with TSC. Consequentially, identifying individuals with TSC who have high levels of these behaviours may facilitate targeting of early interventions to the group of individuals who are at risk of persistent self-injury and aggression, which are likely to have the most pervasive negative impact on well-being.

Given the high rates of ADHD in TSC (Lo-Castro et al. 2011), the role of overactivity/impulsivity in terms of both differentiating persistent self-injury and persistent aggression is of particular note. A growing literature reports an association between impulsivity and self-injury and aggression in individuals with ID, and in those with genetic syndromes (Arron et al. 2011; Davies & Oliver 2016; Richards et al. 2017; Rojahn et al. 2004; Sloneem et al. 2011). In terms of persistence, Richards et al. (2016) demonstrated that this extended to the persistence of self-injury in individuals with ASD. In this study we further demonstrated that impulsivity is associated with persistent self-injury and with persistent aggression. Executive functioning difficulties, specifically in regulating or inhibiting behavioural responses, resulting in the repetition of inappropriate responses, have been proposed as an explanatory framework for understanding associations between impulsivity and both-self-injury and aggression (Davies & Oliver 2016; Oliver & Richards, 2015).

The finding that persistence of self-injury and aggression was associated with behavioural indicators of pain adds further weight to the argument that pain may contribute to adverse behavioural outcomes in individuals with ID, and those with TSC specifically (Carr & Owen-DeSchryver 2007; withheld for blind review; withheld for blind review). The current study provides novel evidence that it may contribute to persistence, as well as presence, of self-injury and aggression in children and adults with TSC. The physical manifestations of TSC include several potentially painful health conditions. Given that just under a third of individuals TSC will have profound ID, precluding self-report of pain, there is a clear risk that pain may go undetected and untreated. It is therefore very important for clinicians to be mindful of the possibility of pain in individuals with TSC showing persistent self-injury or aggression. Conversely they should also be mindful that untreated painful

health conditions may be associated with increased risk of persistent self-injury and aggression.

It was surprising that repetitive behaviour was related to persistence of aggression but not self-injury, particularly as Guess and Carr's model of self-injury (1991) conceptualises self-injury as evolving from stereotyped movements. It is possible that this was a consequence of using the total score of the measure of repetitive behaviour which includes a broad range of repetitive behaviours in addition to motor stereotypies. For aggression, repetitive behaviour differentiated not only those with TSC who showed persistent and absent aggression but also those who showed transient and absent aggression. Associations between repetitive behaviour and both presence and severity of aggression have been described in the wider ID population (Oliver at al. 2012; Oliver & Richards 2015) and in those with genetic syndromes (Arron et al. 2011). In the context of TAND, high levels of repetitive behaviours may be anticipated in TSC given the very high prevalence of ASD symptomatology. No other risk markers were able to discriminate between those who never showed a behaviour and those who showed fluctuating behaviour, thus repetitive behaviour may be a particularly sensitive risk marker for aggression in TSC.

It was also surprising that none of the characteristics examined in the current study were associated with the persistence of destructive behaviours. Past research has found that both overactivity/impulsivity and repetitive behaviours are associated with destructive behaviour (Davies & Oliver 2016; Oliver et al. 2012). It might also be anticipated that the model of behavioural dysregulation posited to account for associations between impulsive behaviour and self-injury and aggression may also generalise to destructive behaviour. This suggests that, in terms of factors associated with persistence over three years in TSC, destructive behaviour may dissociate somewhat from self-injury and aggression, behaviours

that showed some broad consistencies in this sample. Further research is needed to explore factors which might be associated with destructive behaviour in TSC.

A limitation of the current study in terms of generalising to the population of individuals with TSC is lack of information about adults with TSC who do not have ID. As outlined in the methods section, we felt it inappropriate to gather informant reports on adults who may have been able to self-report. However, the two groups represented in the current study (adults with ID and children with and without ID), are likely to include the vast majority of those showing self-injury (as well as aggression and destruction). Given the focus of the current study was on persistence rather than prevalence, this is less of a threat to the validity of the conclusions drawn.

A second limitation is the relatively small sample size. TSC is a rare syndrome, and high degree of heterogeneity further limits the number of participants suitable for inclusion in this informant report study. Around three-quarters of the original sample provided information at time two, representing a good return rate. However, low remission rates of the behaviours being investigated mean that numbers of participants within the remission group were too low to conduct meaningful analysis to provide information about what characteristics might relate to remitting self-injury for example. Finally, it is also important to note that where we discuss persistence and remission, that this is just over a three-year period. It is possible that over a longer period of time, patterns of behaviour may indicate relapsing-remitting cycles, or that those with persistent behaviour across three years may show remittance at a later time point.

In summary, this study demonstrates that where children and adults with TSC show self-injury this is likely to be persistent, a finding which also applies broadly to aggression and destruction. There are a number of characteristics that might identify a person as being at particularly high risk for persistent self-injury and two of these characteristics

(overactivity/impulsivity, behavioural indicators of pain) are shared with those who may be at high risk for persistent aggression. These characteristics should therefore flag particularly high risk of adverse behavioural outcomes to those caring for individuals with TSC. Further research is needed to evaluate whether there is a causal association between these putative risk markers and self-injury and aggression. If such causal relationships are identified then targeted interventions, such as treatment for ADHD symptomatology and monitoring and early treatment of painful health conditions, are clearly implicated.

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